REMARKS

Claims 1-4 are pending. Claim 1 has been amended herein.

Claim 1 has been amended to more accurately reflect the claimed invention. Support for the amendment of claim 1 can be found in the originally filed claims, page 3, last 2 lines through page 4, line 19; page 6, lines 6-10, page 12, lines 13-15; page 12, last full paragraph; page 9, lines 9-10; page 4, lines 6-9; page 2, last 5 lines; and page 6, lines 10-14. No new matter has been added.

Pending claims 1-4 considered together with the following remarks are believed sufficient to place the application into condition for allowance. Accordingly, an early and favorable action on the merits is earnestly solicited at present.

Rejections Under 35 U.S.C. § 102

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by **Klein-Nulend *et al.* (Tissue Engineering, vol 4, 1998)** supported by **Sucheston *et al.* (Ohio J. of Science, 1969)**.

Claims 1-4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over **Van Osch *et al.* (Tissue Engineering, 2000)** supported by **Sucheston *et al.* (Ohio J. of Science, 1969)**.

Reconsideration and withdrawal of the above rejections are respectfully requested based on the following considerations.

Legal Standard For Anticipation

The standard for a rejection under 35 U.S.C. § 102(b) is established in MPEP §2131. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. If an independent claim is allowable under 35 U.S.C. § 102, then any claim depending therefrom is also allowable.

The Present Invention

The claimed invention is drawn to a method of proliferating human chondrocytes by co-culturing chondrocytes obtained from a cartilage having perichondrium together with the perichondrium, wherein no non-human animal feeder cells are present. Non-human animal feeder cells are accompanied with problems of bacterial and viral infections.

Distinctions Over the Cited Art

Klein-Nulend *et al.* (Tissue Engineering, vol 4, 1998)

In contrast to the present invention, Klein-Nulend *et al.* is relevant for teaching the differentiation of cartilage from perichondrium tissue. Klein-Nulend *et al.* teach the direct actions of rhOP-1 on perichondrium cells to stimulate chondrocytic differentiation and production of cartilage matrix *in vitro* (see abstract). Thus, in the method of Klein-Nulend *et al.*, human articular perichondrium is not cultured with chondrocytes.

The technical feature of the present invention is directed to proliferation of human chondrocytes comprising the method steps of:

1) a step of collecting human cartilage having perichondrium;

2) a step of treating the cartilage having perichondrium with an enzyme *(this allows the chondrocytes the ability to be fractionated for efficient culture proliferation)* this step is not

taught in the reference of Klein-Nulend *et al.*; and

3) a step of culturing the cartilage obtained in step 2),

wherein the perichondrium of the cartilage having perichondrium of step 1) exists in step 3), and wherein no non-human animal feeder cells are present in step 3) .

Thus step 3) in amended claim 1 requires that the perichondrium from cartilage having perichondrium is not removed and chondrocytes are cultured with perichondrium. This step is not taught in the reference of Klein-Nulend *et al.*

Klein-Nulend *et al.* does not teach:

a. a step of treating the cartilage having perichondrium with an enzyme, nor

b. a step wherein the perichondrium from cartilage having perichondrium is not removed and chondrocytes are cultured with perichondrium.

Therefore, it is submitted that the Klein-Nulend *et al.* reference does not teach each and every limitation of the present claimed invention.

Accordingly, the present invention is *not* anticipated by the Klein-Nulend *et al.* reference of record. Any contention of the USPTO to the contrary must be reconsidered at present.

Van Osch *et al.* (Tissue Engineering, vol 6, 2000)

In contrast to the present invention, Van Osch *et al.* is relevant for teaching the culturing of **rabbit** perichondrium tissue *in vitro*. Van Osch *et al.* teach harvesting of perichondrium cells from New Zealand white rabbits, wherein the perichondrium was cut in small pieces and cultured.

Van Osch *et al.* **(similar to** Klein-Nulend *et al.)* does not teach a step of collecting **human**

cartilage having perichondrium nor a step of treating the cartilage having perichondrium with an enzyme. (*as recited in the Material and Methods section, page 322, last 9 lines*). Treatment with an enzyme, such as collagenase is needed for proliferation of human chondrocytes.

The claimed method is drawn to proliferating human chondrocytes without resorting to non-human animal feeder cells.

Additionally, Van Osch *et al.* does not teach the human perichondrium from cartilage having human perichondrium not removed and human chondrocytes are cultured with human perichondrium as recited in step 3 of amended claim 1.

Therefore, it is submitted that the Van Osch *et al.*. reference does not teach each and every limitation of the present claimed invention.

Accordingly, the present invention is *not* anticipated by or, in the alternative, obvious over the Van Osch *et al.* reference of record. Any contention of the USPTO to the contrary must be reconsidered at present.

Issues under 35 U.S.C. § 103(a)

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Van Osch *et al.* (Plastic and Reconstructive Surgery, 2001),** in view of **Klein-Nulend *et al.* (Tissue Engineering, vol 4, 1998)** and **Van Osch *et al.* (Tissue Engineering, 2000)** supported by **Sucheston *et al.* (Ohio J. of Science, 1969)**.

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Hiroko *et al.* (WO 02/012451)** in view of **Van Osch *et al.* (Tissue Engineering, 2000)** or **Klein-Nulend *et***

***al.* (Tissue Engineering, vol 4, 1998)** and supported by **Yi *et al.* (Abstract. J. Korean Soc. Plastic Reconst. Surg., 2001)**.

Reconsideration and withdrawal of the above rejections are respectfully requested based on the following considerations.

Distinctions Over the Cited Art

Van Osch *et al.* (Plastic and Reconstructive Surgery, 2001)

Van Osch *et al.*(2001) is relevant for teaching the isolation of human auricular cartilage and culturing the isolated chondrocytes in a monolayer, wherein no exogenous feeder cells are present in culture (see Materials and Methods section).

However, Van Osch *et al.* (2001) does not teach culturing chondrocytes with perichondrocytes as claimed.

Van Osch *et al.*(2001) is directed to culturing for **differentiation** and not proliferation as the title indicates. Further, perichondrium of the cartilage did not exist in the culture. There is no teaching that the perichondrium was bonded to their cartilage. In the method of Van Osch *et al.*(2001), even if chondrocytes were contaminated with perichondrium, perichondrium is eliminated by a combination of enzymatic treatment and filtration from chondrocytes to be cultured by the following method. A sampled cartilage is sliced and incubated with pronase E, then with collagenase B (type II collagenase), the resulting medium is filtered with a 100 μm filter to isolate the chondrocytes. (*See*, page 434, left column, line 4 from the bottom to right column, line 7, of Van Osch *et al.*(2001). This outcome is consistent with the results taught in Table II on page 439,

wherein the percentage of cells positive for Collagen II in the expanded human chondrocytes cultured is at best only 35%.

Hiroko *et al.* (WO 02/012451)

Hiroko *et al.* is relevant for disclosing a method of co-culturing human chondrocytes together with perichondrial cells in the chondrogenic stage as feeder cells. And the "perichondrial cells in the chondrogenic stage, as feeder cells" are obtained from a nonhuman mammalian fetus. (*See*, Hiroko *et al.*, at paragraph [0008]).

In contrast, the method of the presently claimed invention is:

"a method to proliferate human chondrocytes comprising the method steps of:

1) a step of collecting human cartilage having perichondrium;

2) a step of treating the cartilage having perichondrium with an enzyme; and

3) a step of culturing the cartilage obtained in step 2),

wherein the perichondrium of the cartilage having perichondrium of step 1) exists in step 3), and wherein no non-human animal feeder cells are present in step 3)".

The method of the presently claimed invention uses "perichondrium" itself instead of "perichondrial cells in the chondrogenic stage." The "perichondrium" used in the method of the present invention is a membrane tissue surrounding a cartilage and obtained from the cartilage which provides chondrocytes to be cultured. The "perichondrium" of the presently claimed invention is not in the chondrogenic stage, as is the tissue utilized in Hiroko *et al.*

Thus "perichondrial cells in the chondrogenic stage, as feeder cells" used in Hiroko *et al.*

and "perichondrium" itself, used in the method of the present invention, are definitely distinguishable from each other. Consequently, Hiroko *et al.* clearly does not teach this essential limitation.

Hiroko *et al.* is entirely silent with regard to the possibility of using a human perichondrium, let alone the employment of material derived from the same origin. A person of ordinary skill in the art, trying to improve the method described in Hiroko et al. would therefore not derive from Hiroko et al., any incentive to switch from non-human feeder cells to the perichondrium itself.

Van Osch *et al.* (Tissue Engineering, Vol 6, 2000)

Applicant contends that the arguments described above with respect to distinctions over the Van Osch *et al.* reference is equally applicable here (and are incorporated herein by reference in their entirety).

Additionally, Van Osch *et al.* cultured the perichondrium without cartilage (see page 322, last 4 lines). Van Osch *et al.* did not digest the tissue with an enzyme and culture all of the elements as claimed.

Klein-Nulend *et al.* (Tissue Engineering, Vol 4, 1998)

Applicant contends that the arguments described above with respect to distinctions over the Klein-Nulend *et al.* reference is equally applicable here (and are incorporated herein by reference in their entirety).

The culturing method of Klein-Nulend *et al.* obtained cells from perichondrium tissue without cartilage (see page 306, last paragraph and Figure 1). In contrast, this method obtained only 100 chondrocytes at the most (see Table 2, page 311).

Advantages of the present invention

The present invention proliferates human chondrocytes wherein the perichondrium from cartilage having perichondrium is not removed and chondrocytes are cultured with perichondrium. By this process, chondrocytes cells increased at least 1 X 10^6 cells from 1 cm^2 of tissue in primary culture and further the cells increased about 1000 times in subculture (see page 13, (c) Subculture section), and most of all cultured cells expressed type II collagen. Regarding the expression of type II collagen, please see Figure 3. A color version of Figure 3 can be presented to the Examiner, showing in more detail and contrast, the expression of type II collagen (if the Examiner deemed it necessary).

Legal Standard for Determining Prima Facie Obviousness

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. 1, 17, 148 USPQ 459,

467 (1966). Second, the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 set forth some rationales that were set established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Here, the Examiner has not appropriately resolved the *Graham* factors, including ascertaining the differences between the prior art and the claims that are at issue, and the rationale in combining the cited references is improper.

The rationale should be made explicit, *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), and the Examiner must interpret the reference as a whole and cannot pick and choose only those selective portions of the reference which support the Examiner's position. *In re Fine,* 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.").

As the M.P.E.P. directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03.

MPEP § 2143.03 recites examples of Basic Requirements of a *Prima Facie* Case of Obviousness and seven exemplary rationales.

Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

However, Applicants fully address these rationales below. According to Applicants analysis below, the Examiner has not met the basic requirements of a prima facie case of obviousness. More specifically, Applicants contend that:

(A) Combining prior art elements according to known methods cited do not yield predictable results yielding increased proliferation of chondrocyte cells by at least 1 X 10^6 cells from 1 cm^2 of tissue in a culture;

(B) Simple substitution of one known method of culturing of chondrocyte cells, does not yield predictable results in regards to the proliferation of human chondrocytes wherein the perichondrium from cartilage having perichondrium is not removed and chondrocytes are cultured with perichondrium;

(C) There is no known technique to improve proliferation of chondrocyte cells wherein one skilled in the art would combine the perichondrium from cartilage with chondrocytes co-cultured for proliferating human chondrocytes;

(D) Applying a known technique as taught Van Osch *et al.* (Plastic and Reconstructive Surgery, 2001) or Hiroko *et al.* (WO 02/012451) do not yield predictable results for said increase in proliferating chondrocyte cells of at least 1 X 10^6 cells from 1 cm^2 tissue in a primary culture;

(E) The Examiner cannot support the conclusion of "obviousness" on the basis "Obvious to try" – there are no predictable methods or models cited by the Examiner that establish a reasonable expectation of success for said methods of proliferating human chondrocytes wherein the perichondrium from cartilage having perichondrium is not removed and chondrocytes are cultured with perichondrium as claimed;

(F) There is no reason or rationale cited by the Examiner that may prompt variations from the disclosure of Van Osch *et al.* (Plastic and Reconstructive Surgery,

2001) or Hiroko *et al.* (WO 02/012451), combined with Klein-Nulend *et al.* (Tissue Engineering, vol 4, 1998) and Van Osch *et al.* (Tissue Engineering, 2000) that would result in the claimed methods of proliferating chondroctyes.

(G) There is no proper rationale, teaching, suggestion, motivation, or guidance yielding predictable results in the prior art cited by the Examiner that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed method of proliferating human chondrocytes by co-culturing chondrocytes obtained from a cartilage having perichondrium together with the perichondrium.

Accordingly, the present invention is *not* rendered obvious in view of the teachings and disclosures of the cited **Van Osch *et al.* (Plastic and Reconstructive Surgery, 2001)** or **Hiroko *et al.* (WO 02/012451)**, taken with the **Klein-Nulend *et al.* (Tissue Engineering, Vol 4, 1998)** and **Van Osch *et al.* (Tissue Engineering, 2000)** references of record. Any contentions of the USPTO to the contrary must be reconsidered at present.

CONCLUSION

If the Examiner has any questions or comments, please contact Eggerton A. Campbell, Ph.D., Registration No 51,307, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated:

Respectfully submitted,

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